

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A01N 43/50	A1	(11) International Publication Number: WO 99/45779 (43) International Publication Date: 16 September 1999 (16.09.99)
(21) International Application Number: PCT/US99/04651 (22) International Filing Date: 11 March 1999 (11.03.99) (30) Priority Data: 60/077,660 11 March 1998 (11.03.98) US (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US). (72) Inventor; and (75) Inventor/Applicant (for US only): VENKATESH, Gopadi, M. [US/US]; 544 General Learned Road, King of Prussia, PA 19406 (US). (74) Agents: McCARTHY, Mary, E. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW 2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).		(81) Designated States: AE, AL, AU, BA, BB, BG, BR, CA, CN, CZ, EE, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: NOVEL COMPOSITIONS OF EPROSARTAN (57) Abstract This invention relates to a novel composition comprising eprosartan, or a salt, solvate, or hydrate thereof, in particulate form, a process for its production and methods of using the composition to block angiotensin II receptors and to treat hypertension, congestive heart failure and renal failure.		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece			TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
CM	Cameroon			PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakhstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LJ	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

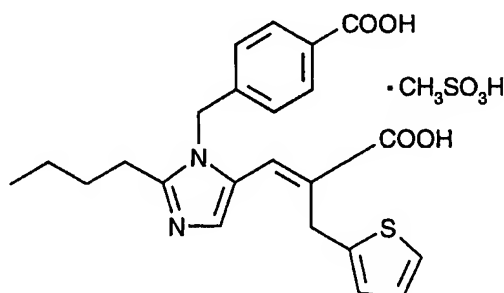
NOVEL COMPOSITIONS OF EPROSARTAN

Field of the Invention

This invention relates to novel compositions of (E)- α -[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid [eprosartan] or its methanesulfonate salt [eprosartan mesylate], and to the use of such compositions in therapy to block angiotensin II (AII) receptors and in the treatment of hypertension, congestive heart failure and renal failure.

Background of the Invention

The compound, (E)- α -[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic, is known by the name "eprosartan" and is the subject of U.S. Patent No. 5,185,351 (the '351 patent), issued February 9, 1993. This patent discloses a process for making the anhydrous form of (E)- α -[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid and its methanesulfonate salt. Additionally, the '351 patent discloses conventional techniques for formulating (E)- α -[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl]methylene-2-thiophenepropionic acid. Eprosartan mesylate has the following structure:



This compound is claimed to have utility in blocking angiotensin II receptors and to be useful in the treatment of hypertension, congestive heart failure and renal failure.

It is known that pharmaceutically active compounds may be subjected to milling procedures to obtain a particle size appropriate for tablet formation and for other formulation types. Air jet milling and fluid energy milling (micronising) have been favoured because of the reduced risk from introducing contamination from mill materials. However, wet milling processes have been proposed for preparation of finely divided particles for pharmaceutical use, for example see U.S. Patent No. 5,145,684. This patent discloses a wet milling procedure to produce particles of a crystalline drug substance having a surface modifier adsorbed on the surface thereof in an amount sufficient to maintain an effective average particle size of less than about 400 nm. This particulate composition as a stable suspension is said to provide improved bioavailability for poorly water soluble compounds.

According to the instant invention, it has been found that eprosartan, or its salts, solvates, or hydrates, can be formulated in novel compositions that have a 2-5 fold enhanced therapeutic activity over that of conventionally-prepared immediate release tablet formulations of the same compound. These novel compositions have enhanced bioavailability.

5

Summary of the Invention

The present invention is based on the finding that (E)- α -[2-n-butyl-1-[(4-carboxyphenyl)methyl]-1H-imidazol-5-yl)methylene-2-thiophenepropionic acid, or its salt forms, such as the mesylate, have enhanced bioavailability in certain compositions of controlled particle size. Anhydrous eprosartan, or its salts, or its solvates or hydrates, may be used in the compositions of the instant invention.

The present invention provides novel compositions comprising eprosartan, or a salt, solvate, or hydrate thereof, in particulate form, said composition having a particle size distribution such that the median value of the volume mean diameter is within the range of from 450 to 700 nm.

This invention also provides a process or a method of producing such compositions in a reproducible manner for the treatment of diseases in which blockade of angiotensin II receptors is indicated, for example, in the treatment of hypertension, congestive heart failure and renal failure.

20

Description of the Invention

According to the present invention, compositions comprising eprosartan, or its salt, are provided in particulate form, such as immediate release (IR) capsules and immediate release/delayed release/ modified release tablets. The compositions are prepared using a process that involves a wet milling step in order to produce a particle size distribution of eprosartan, or its salt, with a volume average median diameter in the range of 450-700 nm. The particulate suspension, thus produced, is spray dried using a spray dryer or granulated using a fluid bed granulator. Compositions are prepared by admixture and, thus, they are suitably adapted for oral, parenteral or pulmonary administration. The compositions may be in the form of tablets, capsules, reconstitutable powders or suppositories. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for mass therapy.

To assist in further processing, that is the preparation of pharmaceutical compositions for therapeutic use, such as capsules and tablets, the wet milling of eprosartan, or its salt, takes place in an aqueous medium containing one or more pharmaceutically acceptable water-soluble carriers suitable for spray drying. The aqueous suspension may optionally contain a surfactant to maintain the particles in suspension until administration of the pharmaceutical formulation to a patient. Pharmaceutically acceptable excipients most suitable for spray-drying are water

soluble hydroxypropylmethyl cellulose, a binder, and mannitol, but other binders, such as polyvinylpyrrolidone (PVP), hydroxypropyl cellulose (HPC), and methyl cellulose, or other carbohydrates, such as sucrose, sorbitol, lactose, lactitol and xylitol and starch may also be used as a carrier.

5 In the aqueous medium to be subjected to the milling, eprosartan, or its salt, may be present from about 10 to about 40% w/w. In practice, 20% w/w drug loading provides an effective compromise between the desire for a high throughput and short milling times.

 The amount of the primary carrier, such as hydroxypropylmethyl cellulose (HPMC), may vary from about 2 to about 20% w/w of the composition to be milled. The secondary
10 carrier, such as mannitol, may also be added to the suspension prior to milling or dissolved in the milled suspension prior to spray drying. Preferably, the total amount of the soluble carrier(s) does not exceed 100% by weight of eprosartan, or its salt, to be processed. For an eprosartan loading of about 20% w/w, an amount of HPMC from about 4 to 12% w/w has been found to be effective, and an amount of about 6% w/w is preferred.

15 The amount of surfactant/glidant, if present, may be varied from about 0.1 to about 0.4% w/w of the aqueous medium. Preferably, it is present at about 1% by weight of eprosartan, or its salt. Suitable surfactants are sodium laurel sulphate and tween 80, while suitable glidants are silicon dioxide and talc.

 The compositions of this invention are most suitably prepared by wet milling
20 eprosartan, or its salt, preferably using a bead mill such as Premier HML Laboratory Supermill manufactured by Premier Mill Corporation, Reading, PA. The milling medium consists of zirconium oxide beads. Bead mills manufactured by others such as Dena Mill by Dena Systems BK Ltd., Barnsley, England, can be used for wet milling eprosartan, or its salt. The particle size distributions of the suspension formulations were determined using a Malvern laser diffraction
25 unit, Master Sizer S Model S4700, from Malvern Instruments Ltd., Malvern, England. Any other laser diffraction particle sizer with sufficient sensitivity and resolution for nanoparticulates can be used. The particles of eprosartan, or its salt, are typically present with not less than 50% of the particles having a volume average diameter of 1000 nm or below. In a preferred embodiment of the invention, the volume averaged median diameter is in the range of
30 450 to 700 nm. In this median range, effective compositions are obtained when 90% of the particles have a volume averaged diameter of 1200 nm or below.

 Using the milling beads and aqueous carrier system described above, a composition having the preferred particle size distribution may be obtained surprisingly quickly, for example, after milling 2.5 kg suspension in the mill for an hour. Increasing milling time, for
35 example, by fivefold, enables the largest particles to be reduced so that at least 90% of particles have a volume average diameter of less than 1000 nm. However, the effect on the median value is marginal, so longer milling times are not cost effective.

Spray drying/fluid bed granulation of milled compositions is carried out most suitably using a spray dryer such as Yamato GA-32 Spray Dryer [Yamato Scientific America Inc., Orangeburg, NY], or a fluid bed granulator, such as Glatt fluid bed granulator.

Tablets and capsules for oral administration are usually presented in a unit dose, and
5 contain conventional excipients such as binding agents, fillers and diluents (tableting or compression aids), lubricants, disintegrants, colorants, flavourings, and wetting agents. The tablets may be coated according to techniques well known in the art.

Suitable binders include polyvinylpyrrolidone (PVP), hydroxypropylmethyl cellulose and pregelatinized starch (Starch 1551). Suitable fillers include microcrystalline cellulose,
10 mannitol, lactose and other similar agents. Suitable disintegrants include super disintegrants such as cross linked polyvinylpyrrolidone (Crospovidone XL), sodium starch glycolate (Explotab) and croscarmellose sodium (Ac-Di-Sol). Suitable lubricants include stearic acid and magnesium stearate.

These solid oral compositions may be prepared by conventional methods of
15 blending, filling, tableting, or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, well known in the art.

Oral formulations also include conventional controlled release formulations, such as tablets or pellets, beads or granules, having a sustained release or an enteric coating, or
20 otherwise modified to control the release of the active compound, for example by the inclusion of gel forming polymers or matrix forming waxes.

Advantageously, a surfactant or wetting agent may be included in the composition to facilitate uniform distribution of the compound of the invention.

Thus, the present invention provides a novel composition which comprises
25 eprosartan, or its salts, solvates, or hydrates. The composition is adapted for oral administration. The composition is presented as a unit dose. Such a composition is taken preferably from 1 to 2 times daily. The preferred unit dosage forms include tablets or capsules. The compositions of this invention may be formulated by conventional methods of admixture such as blending, filling and compressing. Suitable pharmaceutically acceptable
30 carriers for use in this invention include diluents, fillers, binders and disintegrants.

Eprosartan, or its salts, solvates, or hydrates, may be co-administered with other pharmaceutically active compounds, for example, in physical combination or by sequential administration. Conveniently, the compound of this invention and the other active compound are formulated in a pharmaceutical composition. Thus, this invention also relates to
35 pharmaceutical compositions comprising eprosartan, or its salts, solvates, or hydrates, a pharmaceutically acceptable carrier, and a second pharmaceutically active compound selected from the group consisting of a diuretic, a calcium channel blocker, a β -adrenoceptor blocker, a renin inhibitor, and an angiotensin converting enzyme inhibitor. Examples of

compounds which may be included in pharmaceutical compositions in combination with eprosartan, or its salts, solvates, or hydrates, are diuretics, particularly a thiazide diuretic, such as hydrochlorothiazide, or a loop diuretic, such as furosemide, calcium channel blockers, particularly dihydropyridine antagonists, such as nifedipine, β -adrenoceptor
5 blockers, such as propranolol, renin inhibitors, such as enalkinen, and angiotensin converting enzyme inhibitors, such as captopril or enalapril.

No unacceptable toxicological effects are expected when eprosartan, or its salts, solvates, or hydrates is administered in accordance with the present invention.

Eprosartan, or its salts, solvates, or hydrates is useful for treating diseases in which
10 blockade of the angiotensin II receptor would be beneficial. Preferably, this compound is used alone or in combination with said second pharmaceutically active compounds in the treatment of hypertension, congestive heart failure and renal failure. Additionally, eprosartan, or its salts, solvates, or hydrates, is of value in the treatment of left ventricular hypertrophy regression, diabetic nephropathy, diabetic retinopathy, muscular degeneration,
15 haemorrhagic stroke, primary and secondary prevention of infarction, prevention of atheroma progression and the regression of atheroma, prevention of restinosis after angioplasty or bypass surgery, improving cognitive function, angina, glaucoma, and CNS disorders, such as anxiety.

20 The following examples are illustrative of the instant invention. These examples are not intended to limit the scope of this invention as defined hereinabove and as claimed hereinbelow.

Examples of Nanoparticulate Suspensions

25 Suspensions (refer to Table 1 for formulation details) were prepared by dispersing hydroxypropylmethylcellulose (HPMC) in purified water, using a suitable mixer and stored overnight to hydrate. The drug substance was dispersed using a homogenizer and mixing continued until no drug agglomerates remained. The Premier bead mill was set up with 0.6-0.8
30 mm zirconium oxide beads filling about 80% of the milling chamber. The bead mill was operated in accordance with the manufacturer's instructions at the settings listed in Table 1.

After milling, the particle size distribution of the suspensions of Formulas 1-3 was measured using the Malvern laser diffraction unit. The sample was appropriately diluted, and the particle sizer was operated in accordance with the manufacturer's instructions at the settings
35 listed in Table 1. The results are reported in Table 1 as D(0.1), D(0.5), and D(0.9). D(0.1) represents the size (as number average diameter) below which 10% of the particles lie, D(0.5) is the size below which 50% of the particles lie, also known as the median. D(0.9) is the measurement below which 90% of the particles lie.

Examples of Bioenhanced Oral Solid Formulations

The milled suspension was spray dried using a laboratory scale Yamato GA-32 Spray
5 Dryer. The spray dryer was operated in accordance with the manufacturer's instructions at the
settings listed in Table 1. In this apparatus, the milled aqueous suspension was fed by a
peristaltic pump into the drying chamber as an atomized spray. The resulting spray dried
powder was further dried [for example, oven drying at about 40°C] to produce a dry powder
composition which has good flowability/ compactibility properties and hence, is suitable for
10 filling into hard gelatin capsules (Formulas 3 - 5 in Table 1).

The milled suspension was spray granulated in a fluid bed granulator. The fluid bed
contained the excipients listed in Table 2 (Formulas 6 and 7). These granulations were blended
with a disintegrant and a lubricant and compressed into pharmaceutically elegant tablets.

The spray dried material was further wet granulated using a high shear granulator and
15 compressed into tablets by incorporating widely used excipients (Formula 8 in Table 2).

Bio-Equivalence Studies

Test dogs were administered orally in a four-arm study using a dose of 10 mg of
20 eprosartan as zwitterion per kg. The internal granules of the current product (refer to Table 3
for formulation details) was used as the control.

Bio-equivalence studies to determine the relative bioavailability of oral bioenhanced
formulations in healthy volunteers were performed. The study design comprised an open,
randomised, and crossover. A single oral 200 mg dose of the following formulations - a
25 commercial tablet, a capsule of Formula 6 and a tablet of Formula 7. On each of the dosing
days subjects were to receive a single oral dose, with a washout of at least 6 days between
doses. Doses were administered orally with 200 mL water, following a standard breakfast.
The blood samples were collected at predetermined time points and tested.

From the plasma concentration profiles obtained from the clinical studies both in dogs
30 and humans, AUC_{max} (mg.hr/ml) [area under the plasma concentration vs. time curve], C_{max}
(mg/ml) [maximum plasma concentration] and t_{max} (time in hours to achieve maximum plasma
level) were calculated. The results, subjected to appropriate statistical tests, showed an increase
in blood levels by 2-5 fold, when dosing with capsules/tablets containing the bioenhanced
formulations.

Table 1 : Bioenhanced Suspension Formulations

Ingredients	Nanoparticulate suspension formulations - % w/w				
Formula #	1	2	3	4	5
Eprosartan mesylate	10	20	15.7	14.8	14.4
HPM cellulose	10	10	5.9	5.5	1.5
Mannitol				5.5	6.2
Sodium lauryl sulfate					
Purified water	to	to	to	to	to
(ml)	100	100	100	100	100
Parameter	Bead milling conditions				
Bead size, mm	0.6-0.8	0.6-0.8	0.6-0.8	0.6-0.8	0.6-0.8
# passes	2	5	5	10	10
Parameter	Malvern Particle size Distribution				
D(0.1) in nm	181	123	117	98	101
D(0.5) in nm	759	671	643	497	469
D(0.9) in nm	1200	1050	1097	893	879
Parameter	Spray drying conditions				
Inlet temp.(°C)			125	125	125
Outlet temp.(C)			76	78-84	78-84
Air flowrate (m3/min)			0.35	0.45	0.45
Atom. press (kg/cm2)				1.5	1.5
Feed rate (ml/min)			2	5	5

Table 2 : Bioenhanced Tablet Formulations

Ingredients	mg/capsule or mg/tablet		
	6-Capsule	7-Fluid bed	8-High shear
Bead milling Susp.			
Eprosartan mesylate	245.27	245.27	245.27
HPMC (Methocel E5) NF	91.98	91.98	91.98
Silicon dioxide	5.01	5.01	5.01
Purified water USP	*	*	*
Fluid bed bulking			**
Impalpable Lactose	57.74	47.74	47.74
Microcrystalline cellulose		26.01	26
Crosslinked PVP USP		8	8
Externals			
Crosslinked PVP USP			
Magnesium stearate			

* Water is eliminated during spray drying

Table 3 : Formula of Eprosartan Commercial Product

	<u>Ingredients</u>	<u>% w/w</u>
5	Intragranular	
	Eprosartan mesylate (400 mg as zwitterion)	61.32
	Lactose, Monohydrate (Impalpable) NF	3.59
	Microcrystalline cellulose (Avicel PH102) NF	3.59
	Pregelatinized starch (Starch 1551) USP	3.59
	Purified water USP	4.36*
10	Extragranular	
	Croscarmellose sodium (Ac-Di-Sol)	4.00
	Microcrystalline cellulose (Avicel PH102) NF	19.
	Magnesium stearate NF	0.75
	Tablet core weight (200 mg)	400.00
15	Film coating	
	Opadry Blue OY-S-20900**	

a A control tablet formulation was produced by a high shear Fielder granulation and the weight average median diameter of the drug substance (eprosartan mesylate) was ~ 15 microns.

* Purified water is added during granulation to form the dihydrate of the salt.

** Film coat is applied to a level of approximately 2.5-4% of core weight.

It is to be understood that the invention is not limited to the embodiments illustrated hereinabove and the right is reserved to the illustrated embodiments and all modifications coming within the scope of the following claims.

What is claimed is:

1. A pharmaceutical composition comprising eprosartan, or a salt, solvate, or
5 hydrate thereof, in particulate form, said composition having a particle size distribution
such that the median value of the volume mean diameter is within the range of from 450
to 700 nm.
2. The composition according to claim 1 wherein eprosartan, or a salt, solvate,
10 or hydrate thereof, is eprosartan mesylate.
3. The composition according to claim 1 which is produced by wet milling
eprosartan, or a salt, solvate, or hydrate thereof, in the presence of water and
pharmaceutically acceptable excipients.
15
4. The composition wherein the excipient is hydroxypropylmethyl cellulose or
mannitol.
5. A process for the preparation of the composition according to claim 1 in
20 which the eprosartan, or a salt, solvate, or hydrate thereof, in particulate form, is produced
by milling eprosartan, or a salt, solvate, or hydrate thereof, using a bead mill in the presence
of hard zirconium oxide beads, water and hydroxypropylmethyl cellulose, optionally adding
one or more pharmaceutically acceptable excipients, spray drying and filling the resulting
powder into capsules.
25
6. A method of blocking angiotensin II receptors which comprises
administering to a subject in need thereof an effective amount of the composition according
to claim 1.
- 30 7. A method of treating hypertension which comprises administering to a
subject in need thereof an effective amount of the composition according to claim 1.
8. A method of treating congestive heart failure which comprises administering
to a subject in need thereof an effective amount of the composition according to claim 1.
35
9. A method of treating renal failure which comprises administering to a
subject in need thereof an effective amount of the composition according to claim 1.

10. A method of treating hypertension which comprises administering stepwise or in physical combination the composition according to claim 1 and a second pharmaceutically active compound selected from the group consisting of a diuretic, a calcium channel blocker, a β -adrenoceptor blocker, a renin inhibitor, and an angiotensin converting
5 enzyme inhibitor.
11. The method according to claim 10 wherein the second pharmaceutically active compound is a diuretic.
- 10 12. The method according to claim 11 wherein the diuretic is hydrochlorothiazide.
13. The use of a composition according to claim 1 for the treatment of diseases in which blockade of the angiotensin II receptor is indicated.
15
14. The use of a composition according to claim 1 for the treatment of hypertension.
15. The use of a composition according to claim 1 for the treatment of
20 congestive heart failure.
16. The use of a composition according to claim 1 for the treatment of renal failure.
- 25 17. The use of a composition according to claim 1 in combination with a diuretic for the treatment of hypertension.
18. The use according to claim 17 wherein the diuretic is hydrochlorothiazide.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/04651

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A01N 43/50

US CL :514/400

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/400

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
NONE

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Extra Sheet.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	Database EMBASE on STN, No. 95358928, Medicinal Chemistry Department, Istituto S. LusoFarmaco, Milano, Italy, Salmbeni et al., "N-3-substituted pyrimidinones as potent, orally active, AT1 selective angiotensin II receptor antagonists", Abstract to Journal of Medicinal Chemistry 1995, 38/24, pp. 4806-4820	1-18
Y	Database TOXLIT on STN, No. 1994:35332, Dep. Renal Pharmacol., Smithkline Beecham Pharm., Brooks et al. "Blood pressure lowering activity of enalapril and the nonpeptide angiotensin II receptor antagonist, SK&F 108566, in furosemide-treated conscious cynomolgus monkeys. Abstract to Pharmacol. Commun., 1993, Vol. 2, No. 4, pp. 331-337.	1-18



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

27 JULY 1999

Date of mailing of the international search report

17 AUG 1999

Name and mailing address of the ISA/US
Commissioner of Patents and Trademarks
Box PCT
Washington, D.C. 20231

Facsimile No. (703) 305-3230

Authorized officer?

DWAYNE C. JONES

Telephone No. (703) 308-0196

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/04651

B. FIELDS SEARCHED

Electronic data bases consulted (Name of data base and where practicable terms used):

CAPLUS, MEDLINE, BIOSIS, KIFESCI, BIOTECHDS, WPIDS, CONFSCI, JICST-EPLUS, PROMT, TOXLIT, TOXLINE, DRUGU, DRUGL, DRUGLAUNCHI search terms include: eprosartan, angiotensin II receptor?, admin?, (A2 or AII or A12 or AIII)(s)(angiotensin or angio) tensin) or (angiotensin or angio tensin)(2W)(II or 2), inhibit? or block?, (high(w)(blood or bp) or (hbp or bp) or (hbp or bp)(5a)(blood or hypertens? or hyper tens? or blood pressure orrenal? or kidney, treat? or therap? or prevent?